ONO PHARMACEUTICAL CO.,LTD.

January 8, 2019

ONO Receives Manufacturing and Marketing Approval in Japan for Demser® Capsule, a Tyrosine Hydroxylase Inhibitor, for Improvement of Status of Catecholamine Excess Secretion in Patients with Pheochromocytoma

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") announced today that it received a manufacturing and marketing approval of Demser® (metyrosine) Capsule 250 mg ("Demser"), a tyrosine hydroxylase inhibitor, in Japan for the improvement of status of catecholamine excess secretion in patients with pheochromocytoma.

Pheochromocytoma (PC) is a neuroendocrine tumor deriving from the adrenal medulla or the extra-adrenal gland ganglion with 2,920 patients estimated in Japan*. Catecholamine excessively secreted from PC causes various symptoms, such as tachycardia, headache, palpitation, sweating, constipation, including hypertension. Sympatholytic drugs, α-blocker and β-blocker, for control of blood pressure and heart rate have been usually used to improve these symptoms. As there are many cases where surgical removal of tumors is not applicable in patients with locally invasive or metastatic malignant PC, a long-term therapy, such as radiotherapy and chemotherapy is required. The chronic continuation of catecholamine excess secretion may increase a risk of causing cardiovascular-related adverse events such as heart failure or fatal arrhythmia.

Demser inhibits tyrosine hydroxylase related to the production of catecholamine, reduces catecholamine extremely secreted from PC, and alleviates symptoms due to catecholamine excess secretion. Demser is a promising drug with an efficacy in the improvement of the symptoms in patients who are not able to sufficiently control the symptoms with sympatholytic drugs.

Demser is a product for which development companies were recruited in Japan at the "Review Committee on Unapproved or Off-label Drugs with High Medical Needs", established by the Ministry of Health, Labour and Welfare (MHLW), and ONO has been developing this product. In May 2015, the product was designated for the orphan drug by the MHLW.

ONO obtained exclusive rights to develop and commercialize metyrosine in Japan for the treatment of PC (and conditions and symptoms related thereto), in accordance with the license agreement concluded in October 2013 with Valeant Pharmaceuticals North America LLC, an affiliate of Valeant Pharmaceuticals International, Inc. (In July 2018, the company name was changed to Bausch Health Companies Inc., "Bausch Health"). In the US, Bausch Health markets the product under the tradename of "Demser®" in the indication of PC.

*: "Actual condition survey and preparation of medical guideline of pheochromocytoma" Research Report 2009, Research Project on Overcoming Intractable Diseases Project being conducted by the Ministry of Health, Labour and Welfare

Overview of Demser® Capsule 250 mg

Product Name	Demser® Capsule 250 mg
Generic name (JAN)	Metyrosine
Indication	Improvement of status of catecholamine excess secretion in patients with pheochromocytoma
Dosage and administration	Usually, for adults and children 12 years of age and older, start to administer 500 mg of metyrosine orally daily. When the effect is insufficient, titrate the dose by 250 mg or 500 mg daily at intervals of 3 days or more by monitoring the clinical course closely, and dosage should be adjusted under adequate observation of urinary catecholamine amount and symptoms of the patient. However, the maximum daily dose is 4,000 mg with the highest dose of 1,000 mg per dose at intervals of 4 hours or longer. The daily dose of 500 mg is divided twice a day, 750 mg three times a day and 1,000 mg four times a day.
Manufacturer/distributor	Ono Pharmaceutical Co., Ltd.
Approval date	January 8, 2019
Conditions for approval	1. Risk Management Plan should be designed appropriately implemented. 2. Because of the very limited number of patients treated with the product in Japanese clinical trials, a post-marketing use-results survey covering all cases should be performed until data on a certain minimum number of patients have been accumulated. Through these activities, actions necessary to ensure the proper use of the product should be taken by identifying the characteristics of patients to be treated with the product and collecting safety and efficacy data as soon as possible.

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